Correlation of Microalbuminurina and Estimated Glomerular Filtration Rate in Hypertensive Patients

Raghav R Nagpal, Purva Bawikar, Jaishree Ghanekar

ABSTRACT
Microalbuminuria has been shown to be an intermediate end point and a powerful predictor of morbidity and mortality in patients with diabetes. This study aims to analyze the correlation between microalbuminuria and estimated glomerular filtration rate (eGFR) in hypertensive nondiabetic patients, to understand the role of microalbuminuria as a disease marker in hypertensive renal disease. Data of 100 patients meeting the inclusion and exclusion criteria were collected. Early screening of patients with hypertension, for microalbuminuria, by carrying out simple, inexpensive tests like urinary dipstick and spot urinary albumin/creatinine ratio, can help prompt the physician to initiate antihypertensive therapy in positive cases. Prevalence of microalbuminuria, which is an indicator of early chronic kidney disease (CKD), is about 49% among patients with hypertension.

KEYWORDS: Estimated glomerular filtration rate, Hypertensive renal disease, Microalbuminuria, Urinary albumin/creatinine ratio.

INTRODUCTION
Microalbuminuria (MA) is typically defined as a 24 hours urinary albumin excretion rate of 30–300 mg (>20 to <200 µg/min) or Urinary albumin/creatinine ratio (UACR) of 2.5–30 mg/mmol in men, 3.5–30 mg/mmol in women 1 (Table 1).

For several years, the gold standard for measurement of MA was protein quantification of a 24-hour urine collection. Collection errors and inconvenience have eliminated this approach for screening purposes.2 The use of an early morning “spot” urine albumin-creatinine measurement (expressed as mg of albumin per gram creatinine) performed three times within a few weeks has been validated as an appropriate way to assess whether MA is present or not.3,4 The National Kidney Foundation Disease Outcomes Quality Initiative (DOQI) guidelines recommend an untimed spot urine sample, with a preference for first morning samples.5 A variety of antibody-based methods are available to measure urinary albumin. These include radioimmunoassay (RIA), nephelometry, immuno-turbidimetry, and enzyme-linked Immuno-absorbent assay (ELISA). A more accurate high-performance liquid chromatography (HPLC) method that is more sensitive to detect microalbuminuria has been developed recently.6-8

Microalbuminuria (MA) can be reduced, and progression to overt proteinuria prevented, by aggressive blood pressure reduction, especially with a regimen based on medications that block the renin-angiotensin-aldosterone system, and control of diabetes.

The National Kidney Foundation recommends that blood pressure levels be maintained at or below 130/80 mm Hg in anyone with diabetes or kidney disease. Clinical studies have shown that small increases in micro-albuminuria indicate worsening cardiovascular disease, involving endothelial dysfunction and accelerated atherosclerosis, and are associated with significant increases in the risk of end-organ damage, major CV events and death.7,8

Microalbuminuria is an independent predictor of hypertension, metabolic syndrome, type 2 diabetes and coronary artery disease.9-11

Microalbuminuria develops from progressive, subclinical, structural and functional changes within the kidney and represents a sensitive marker of early renal disease.10,11 Microalbuminuria is reported to be present in approximately 30–40% of patients with hypertension and appears to correlate both with severity and duration of hypertension.12,13

The Losartan Intervention for endpoint reduction in hypertension (LIFE) study14 confirmed the predictive power of microalbuminuria and its changes over time15 in a large cohort of carefully monitored patients during a 5-year follow-up; however, the renal predictive value of albuminuria is thus far limited to high-risk patients with or without diabetes.16,17

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**Table 1:** Proteinuria vs. microalbuminuria

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Microalbuminuria</th>
<th>Normal</th>
<th>Microalbuminuria</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine protein (mg/24-hour)</td>
<td>24-hour albumin (mg/24-hour)</td>
<td>Albumin/ Creatinine ratio (mg/g)</td>
<td>Dipstick proteinuria</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8–10</td>
<td>&lt;30</td>
<td>Absent</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–300</td>
<td>30–300</td>
<td>Absent / Trace/1+</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>Trace–3+</td>
<td>&gt;150</td>
</tr>
</tbody>
</table>

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Microalbuminuria

A Genova investigation on complications (MAGIC) study,\(^\text{18}\) comprised a total of 1230 patients with primary hypertension who were recruited between 1993 and 1997 and were followed-up for a median of 11.8 years (range 1.6–14.2 years). The study cohort was composed of 917 patients who did not have diabetes and had hypertension and was aged 49 ± 10 years (median 51 years) without previous cardio-renal events or known renal disease.

At baseline, microalbuminuria was present in 36% of those who developed chronic renal insufficiency (CRI) compared with only 7% of control subjects. Patients who had hypertension and developed chronic renal insufficiency were older and showed higher BP levels and worse renal function than those who remained free from renal endpoints. Patients with microalbuminuria were more likely to be males and showed higher BP and higher serum uric acid levels as compared with patients without microalbuminuria, despite similar renal function and lipid profile.

Microalbuminuria has been shown to be an intermediate endpoint and a powerful predictor of morbidity and mortality in patients with diabetes. In particular, the degree of albuminuria is strongly related both to the progression of diabetic renal disease and to the risk for cardiovascular events.\(^\text{19}\)

The overall prevalence of MA in another study conducted in Kottayam Medical College, in patients with essential hypertension was 26.67%,\(^\text{20}\) which was slightly higher than the prevalence of MA observed (23%) in the LIFE study.\(^\text{21}\)

MATERIAL AND METHODS

A cross-sectional cohort study was conducted in hypertensive patients, either visiting outpatient department (OPD) or getting admitted to MGM Hospital, Kamathe, Navi Mumbai, Maharashtra, India, between November 2015 to November 2017 after the approval from the institutional ethics committee. Written informed consent was taken from patients or their respective relatives, satisfying the study criteria. Inclusion and exclusion criteria are shown below. Operational Definitions

- Newly diagnosed hypertensive: History of hypertension less than 1 month.
- Recently diagnosed hypertensive: History of hypertension from 1 month to 1 year.
- Cockroft Gault formula for eGFR (mL/min): \((140–\text{age}) \times \text{Weight} \div 72 \times \text{Creatinine}\)

For females, multiply result by 0.85
- MDRD-IV Formula for eGFR (mL/min): \(186.3 \times \text{Cr}^{-1.154} \times \text{age}^{-0.203} \times \text{GNF} \times \text{ET}_{F}\)

\(\text{GNF}—\text{Gender factor (male} = 1; \text{female} = 0.742)\)

\(\text{ET}_{F}—\text{Ethnicity factor (white, non black} = 1; \text{black race} = 1.212)\)

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group of 25–60 years</td>
<td>Overt proteinuria</td>
</tr>
<tr>
<td>Male and female</td>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Newly detected hypertensive patients</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Known cases of hypertension since 5 years with/without treatment</td>
<td>Urinary tract infections,</td>
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<td></td>
<td>Diabetes mellitus</td>
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<td>Pregnant women</td>
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<td></td>
<td>Obstructive uropathy and nephrolithiasis</td>
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<td>Renovascular hypertension</td>
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<td></td>
<td>Drugs causing hypertension:</td>
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<tr>
<td></td>
<td>Steroids, amphetamines</td>
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<tr>
<td></td>
<td>NSAIDS</td>
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</table>

Table 2: JNC-7 classification of BP for adults aged 25 years or older

<table>
<thead>
<tr>
<th>BP classification</th>
<th>Systolic, mm Hg</th>
<th>Diastolic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>Or 80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>Or 90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>Or ≥ 100</td>
</tr>
</tbody>
</table>

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• **Microalbuminuria**: Positive UACR: Value more than 30–300 mg of albumin per 24 hours (30–300 mg/mg creatinine). Negative UACR: Values less than <30 mg of albumin per 24 hours or <30 mg/g creatinine.

**Study Design**

The study comprised of 100 patients. Patients fulfilling the study criteria were examined clinically and underwent routine investigations for initial evaluation. Patients were categorized on the basis of JNC-7 classification, severity (blood pressure on admission) and duration of hypertension. Three urine samples on three separate occasions were sent for spot UACR. The mean of 3 values of UACR was calculated quantitatively and categorized as UACR positive (≥30 mg/g) or UACR negative (<30 mg/g). The qualitative result of UACR was then correlated with other parameters. Patients with UACR ≥30 mg/g were screened for further end-organ damage.

**RESULTS**

Data were entered and analyzed by Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS) 20.0. Univariate analysis (Chi-square test) was used to determine the relationship between Microalbuminuria and eGFR. Results of the study were expressed as p values.

Graph 1, compare the number of patients belonging to 4 categories of eGFR when calculated by Cockroft Gault and MDRD-IV method. The values of eGFR have been divided into four categories:

- <90 mL/min; 91–130 mL/min; 131–170 mL/min and 171–215 mL/min. Microalbuminuria was evident in patients with an eGFR of <90 mL/min or between 91 mL/min and 130 mL/min calculated either by Cockroft Gault or MDRD-IV formulae. It indicates that patients with hyper-filtration have a protective mechanism and microalbuminuria does not manifest in these patients.

**Chi-square Test**

*Graph 2 and Table 3 Interpretation:* Since p value for the Chi-square test is greater than that of 0.05, and it indicates no significance of the association between eGFR and UACR.

**Chi-square Test**

*Graph 3 and Table 4 interpretation:* Since p value for the Chi-square test is greater than that of 0.05, it indicates no significance of the association between eGFR and UACR.

Graph 4 shows that most of the patients in the study belonged to the G1 stage of KDIGO for chronic kidney damage.

Graph 5 depicts the distribution of patients with microalbuminuria according to GFR (KDIGO Staging of Chronic Kidney Damage, Table 5). Out of the 49 patients with microalbuminuria, 32 patients were in G1 stage, 15 in G2 and one each in G3b and G4.

**Chi-Square Test Result**

*Graph 5, Table 6 interpretation:* Since p value for the chi-square test is less than that of 0.05, it indicates that the proportion of the positive cases is not equal in all the classes. It can be observed from the residual table that the proportion of positive cases is significantly more in G1 and less in G3b and G4.
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**DISCUSSION**

Glomerular filtration rate (GFR) >120 mL/min indicates glomerular hyperfiltration in pre-hypertension, stages 1 and 2 of hypertension. Glomerular hyperfiltration precedes microalbuminuria. Hyperfiltration induces preglomerular arterial vasospasm creating glomerular ischemia, which initially protects and later is compensated by efferent arteriolar constriction to maintain GFR. The GFR then starts dropping with progressive glomerular hypertension, arteriosclerosis, afferent arteriolar dilatation in some glomeruli, and glomerulosclerosis in others respectively, till ESRD develops. Hyperfiltration → Glomerular afferent arteriolar constriction → Ischemia → Efferent arteriolar constriction → Glomerular hypertension → Microalbuminuria.

Saha and Bhattarai et al. in their study, established a positive correlation between eGFR (Cockroft Gault and MDRD-IV) and UACR in cases with diabetes type-2 and primary hypertension. In our study eGFR was calculated by Cockroft Gault and MDRD-IV and these values of eGFR have been divided into four categories as, <90 mL/min, 91–130 mL/min and 131–170 mL/min and 171–215 mL/min, for statistical analysis. Microalbuminuria was evident in patients with a GFR of <90 mL/min or between 91–130 mL/min calculated either by Cockroft Gault or MDRD-IV formulae. But these were statistically insignificant hence association between GFR (Cockroft Gault and MDRD-IV) and UACR could not be established. When GFR was categorized on the basis of KDIGO staging for
CKD, microalbuminuria was most commonly found in G2 stage (57.7% = 15 out of 26), followed by G1 stage (45.07% = 32 out of 71), although the proportion of positive cases was significantly more in G1 stage. Prevalence of microalbuminuria, an indicator of early CKD burden in the community, was 49% among the patients with hypertension. Early screening of patients with hypertension, for microalbuminuria, by doing simple, inexpensive tests like urinary dipstick and spot urinary albumin/creatinine ratio, can help prompt the physician to initiate antihypertensive therapy in positive cases. Early diagnosis and prevention of microalbuminuria might reduce the progression of hypertensive end-organ damage such as stroke, CKD and cardiovascular events in the community. Although eGFR by Cockroft Gault and MDRD-IV methods can give a good estimate of GFR, newer formulas like GFR by EPI cystatin-C and EPI creatinine–cystatin may be better predictors of actual GFR. Nevertheless, in a developing country like India, eGFR by Cockroft Gault and MDRD-IV methods come in handy, for the screening of patients with microalbuminuria, to predict renal and cardiovascular events.

REFERENCES